A complex of cyclohexane-1,2-diaminoplatinum with an amphiphilic biodegradable polymer with pendant carboxyl groups

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1. Introduction

The first generation of platinum-based anticancer drugs such as cisplatin and carboplatin have greatly improved the prognosis for ovarian, lung, and especially testicular cancer patients [1–3]. However, both cisplatin and carboplatin can cause serious side-effects, including renal toxicity, hematological toxicity, peripheral neuropathy, and gastrointestinal side-effects such as nausea and vomiting [4–6]. Thus many novel Pt-based compounds have been developed and are still under investigation with the hope of reducing general toxicity while maintaining or increasing efficacy for tumor killing.

Oxaliplatin (L-OHP) ((1R,2R)-cyclohexane-1,2-diamino)(ethane-dioato-O,O')platinum(II)) is the third generation of Pt anti-cancer compounds which is approved as a first-line chemotherapy drug in combination with 5-fluorouracil for the treatment of advanced colorectal cancers worldwide [7]. Compared with cisplatin or carboplatin, oxaliplatin displays a better tolerability but still has a few side-effects (acute dysesthesias, cumulative peripheral distal neurotoxicity) which limit its range of usable doses [8,9].

In addition to developing low-molecular-weight Pt complexes in order to reduce side-effects, macromolecular Pt complexes have been explored in recent years. They are expected to overcome the side-effects by prolonging the systematic circulation and improving the bio-distribution of the drugs and passively targeting the drugs to the cancerous sites by enhanced permeation and retention (EPR) effect of macromolecules [10–12]. Several polymeric Pt(II) complexes have been prepared, including dextran-immobilized Pt complexes [13], dendrimers containing Pt complexes [14,15], HPMA copolymer conjugates with Pt complexes [16], poly(phosphazene-diamine)-Pt complexes [17,18], and polyaspartamide or polyglutamide Pt complexes [19–21]. However, few have displayed significant benefit in vivo. The polymer carriers in these complexes or conjugates are mostly water-soluble and non-biodegradable. Their accumulation in the human body is harmful to the patient’s health. Because of their molecular chain mobility in an aqueous environment, the Pt complexes are always exposed to the body fluids and not protected effectively, and thus their dissociation in body fluids is unavoidable, often leading to severe side-effects. However, it is notable that Kataoka and his coworkers developed a series of poly(ethylene glycol)-b-poly(aspartic acid) and poly(ethylene glycol)-b-poly(glutamic acid) incorporating cisplatin or (1R,2R)-cyclohexane-1,2-diamino)platinum(II) species (DACH-Pt) [19–21]. It must be pointed out that poly(ethylene glycol)-b-poly(aspartic acid) and poly(ethylene glycol)-b-poly(glutamic acid) are water-soluble polymers which can self-assemble into nano-micelles once Pt atoms work as the metal cross-links. In this way, the Pt agent in the micellar cores could be protected from the body fluids.